Hypothyroidism (primary)

Search date September 2009

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ABSTRACT

INTRODUCTION: Hypothyroidism is six times more common in women, affecting up to 40/10,000 each year (compared with 6/10,000 men). METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for clinical (overt) hypothyroidism? What are the effects of treatments for subclinical hypothyroidism? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found six systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: levothyroxine, and levothyroxine plus liothyronine.

QUESTIONS

INTERVENTIONS

TREATING OVERT HYPOTHYROIDISM

Likely to be beneficial

Unlikely to be beneficial

SUBCLINICAL HYPOTHYROIDISM

Unknown effectiveness

Footnote

*No RCT evidence, but there is clinical consensus that levothyroxine is beneficial in clinical (overt) hypothyroidism. A placebo-controlled trial would be considered unethical.

Key points

- Primary hypothyroidism is defined as low levels of blood thyroid hormone due to destruction of the thyroid gland. This destruction is usually caused by autoimmunity, or an intervention such as surgery, radioiodine, or radiation.

  It can be classified as clinical (overt), when diagnosed by characteristic features, raised levels of thyroid stimulating hormone (TSH), and reduced levels of T_4, or subclinical, when serum TSH is raised, but serum T_4 is normal and there are no symptoms of thyroid dysfunction.

  Hypothyroidism is 6 times more common in women, affecting up to 40/10,000 each year (compared with 6/10,000 men).

- There is consensus that levothyroxine is effective in treating clinical (overt) hypothyroidism, but evidence is sparse.

  Treatment can lead to hyperthyroidism, reduction of bone mass in postmenopausal women, and increased risk of atrial fibrillation.

  We found no evidence from RCTs that levothyroxine plus liothyronine improves symptoms more than levothyroxine alone.

- We don't know how effective levothyroxine is in treating people with subclinical hypothyroidism, as trials have been too small to detect any clinically relevant improvements in outcomes.

DEFINITION

Hypothyroidism is characterised by low levels of blood thyroid hormone. **Clinical (overt) hypothyroidism** is diagnosed on the basis of characteristic clinical features, consisting of mental slowing, depression, dementia, weight gain, constipation, dry skin, hair loss, cold intolerance, hoarse voice, irregular menstruation, infertility, muscle stiffness and pain, bradycardia, hypercholesterolaemia, combined with a raised blood level of thyroid stimulating hormone (TSH) (serum TSH levels >12 mU/L), and a low-serum thyroxine (T_4) level (serum T_4 <60 nmol/L). **Subclinical hypothyroidism** is diagnosed when serum TSH is raised (serum TSH levels >4 mU/L) but serum T_4 is normal, with minor or no symptoms or signs of thyroid dysfunction. **Primary hypothyroidism** occurs after destruction of the thyroid gland because of autoimmunity (the most common cause), or medical intervention such as surgery, radioiodine, and radiation. **Secondary hypothyroidism** occurs after pituitary or hypothalamic damage, and results in insufficient production of TSH. Secondary hypothyroidism is not covered in this review. **Euthyroid sick syndrome** is diagnosed when tri-

iodothyronine (T_3) levels are low, serum T_4 is low, and TSH levels are normal or low. Euthyroid sick syndrome is not covered in this review.

INCIDENCE/ PREVALENCE

Hypothyroidism is more common in women than in men (in the UK, female:male ratio of 6:1). One study (2779 people in the UK with a median age of 58 years) found that the incidence of clinical (overt) hypothyroidism was 40/10,000 women a year and 6/10,000 men a year. The prevalence was 9.3% in women and 1.3% in men. [1] In areas with high iodine intake, the incidence of hypothyroidism can be higher than in areas with normal or low iodine intake. In Denmark, where there is moderate iodine insufficiency, the overall incidence of hypothyroidism is 1.4/10,000 a year, increasing to 8/10,000 a year in people over 70 years. [2] The incidence of subclinical hypothyroidism increases with age. Up to 10% of women over the age of 60 years have subclinical hypothyroidism (evaluated from data from the Netherlands and USA). [3] [4]

AETIOLOGY/ RISK FACTORS

Primary thyroid gland failure can occur as a result of chronic autoimmune thyroiditis, radioactive iodine treatment, or thyroidectomy. Other causes include drug adverse effects (e.g., amiodarone and lithium), transient hypothyroidism due to silent thyroiditis, subacute thyroiditis, or postpartum thyroiditis.

PROGNOSIS

In people with subclinical hypothyroidism, the risk of developing clinical (overt) hypothyroidism is described in the UK Whickham Survey (25 years' follow-up; for women: OR 8, 95% CI 3 to 20; for men: OR 44, 95% CI 19 to 104; if both a raised TSH and positive antithyroid antibodies were present; for women: OR 38, 95% CI 22 to 65; for men: OR 173, 95% CI 81 to 370). For women, the survey found an annual risk of 4.3% a year (if both raised serum TSH and antithyroid antibodies were present) and 2.6% a year (if raised serum TSH was present alone); the minimum number of people with raised TSH and antithyroid antibodies who would need treating to prevent this progression to clinical (overt) hypothyroidism in one person over 5 years is 5 to 8. [1] **Cardiovascular disease:** A large cross-sectional study (25,862 people with serum TSH between 5.1 mU/L and 10.0 mU/L) found significantly higher mean total cholesterol concentrations in people who were hypothyroid compared with people who were euthyroid (5.8 mmol/L *v* 5.6 mmol/L). [3] Another study (124 elderly women with subclinical hypothyroidism, 931 women who were euthyroid) found a significantly increased risk of MI in women with subclinical hypothyroidism (OR 2.3, 95% CI 1.3 to 4.0) and of aortic atherosclerosis (OR 1.7, 95% CI 1.1 to 2.6). [4] **Mental health:** Subclinical hypothyroidism is associated with depression. [5] People with subclinical hypothyroidism may have depression that is refractory to both antidepressant drugs and thyroid hormone alone. Memory impairment, hysteria, anxiety, somatic complaints, and depressive features without depression have been described in people with subclinical hypothyroidism. [6]

AIMS OF INTERVENTION

To eliminate the symptoms of hypothyroidism and maximise quality of life.

OUTCOMES

Symptom severity; **quality of life**; **cognitive function** (evaluated by cognitive function tests, memory tests, reaction time, self-rating mood scales, and depression scores); **cardiac function** (evaluated by echocardiography); **changes in body composition** (measured by osteodensitometry or bioimpedance measurements); **prevention of progression from subclinical to overt hypothyroidism**; and **adverse effects** of treatments (bone mass, fracture rate, CVD [episodes of atrial fibrillation and ischaemic events]; development of hyperthyroidism).

METHODS

Clinical Evidence search and appraisal September 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to September 2009, Embase 1980 to September 2009, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, Issue 3, 2009. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the author for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence

available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments for clinical (overt) hypothyroidism?**

OPTION **LEVOTHYROXINE (L-THYROXINE) FOR CLINICAL (OVERT) HYPOTHYROIDISM**

- For GRADE evaluation of interventions for Hypothyroidism (primary), see table, p 12 .
- We found no direct information from RCTs about whether levothyroxine is better than no active treatment. There is consensus that treatment reduces symptoms.
- Treating clinical (overt) hypothyroidism with thyroid hormone (levothyroxine) may induce hyperthyroidism and increase the risk of atrial fibrillation.

Benefits and harms

Levothyroxine (L-thyroxine) versus placebo:

We found no systematic review or RCTs comparing L-thyroxine versus placebo in people with clinical hypothyroidism, although there is consensus that treatment improves symptoms (see comment below). We found one longitudinal observational study, [7] one systematic review (search date not reported), [8] and one cohort study [9] that reported on adverse effects of levothyroxine.

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fracture rate					
[7] Longitudinal observational study	1180 people	**Fracture rate , 8.6 years (average)** with L-thyroxine with control Absolute results not reported	P value not reported Reported as not significant	⟷	Not significant
Bone mass					
[8] Systematic review	441 pre-menopausal women, average age 40 years 13 RCTs in this analysis Subgroup analysis	**Bone mass , 8.5 years** with L-thyroxine (164 micrograms/day) with control Absolute numbers not reported All women had received prolonged L-thyroxine treatment with reduced serum TSH concentration but normal serum thyroxine (T_4) and tri-iodothyronine (T_3) values	Difference –2.7% P value reported as not significant	⟷	Not significant
[8] Systematic review	317 post-menopausal women, average age 61.2 years 13 RCTs in this analysis Subgroup analysis	**Bone mass , 9.9 years** with L-thyroxine (171 micrograms/day) with control Absolute numbers not reported All women had received prolonged L-thyroxine treatment with reduced serum TSH concentration but normal serum thyroxine	Difference –9.0% 95% CI –2.4% to –15.7%	○○○	control

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		(T_4) and tri-iodothyronine (T_3) values			
Atrial fibrillation					
[9] Cohort study	1637 people aged >60 years, serum TSH concentrations 0.1 mU/L or less	**Increased risk of atrial fibrillation (diagnosed by electrocardiogram) , 10 years** 28 per 1000 person-years with low serum TSH concentrations (0.1 mU/L or less) 11 per 1000 person-years with normal TSH values	P = 0.005	○○○	normal TSH values
[9] Cohort study	1637 people aged >60 years, serum TSH concentrations 0.1 mU/L or less	**Atrial fibrillation event rate , 10 years** 13/61 (21%) with low serum TSH concentrations (0.1 mU/L or less) 133/1576 (8%) with normal TSH values Exclusion of people who received thyroid hormone therapy (36/61 with low TSH and 46/1576 with normal TSH) from the analysis did not affect the RR. The risk of atrial fibrillation was related to reduced serum TSH and not to thyroid hormone therapy itself	RR adjusted for other known risk factors 3.1 95% CI 1.7 to 5.5	●●○	normal TSH values

Levothyroxine (L-thyroxine) versus L-thyroxine plus liothyronine:

See levothyroxine (L-thyroxine) plus liothyronine, p 4 .

Further information on studies

Comment: There is consensus that treatment with L-thyroxine improves symptoms. A placebo-controlled trial would be considered unethical. Over-treatment with L-thyroxine may cause hyperthyroidism.

OPTION LEVOTHYROXINE (L-THYROXINE) PLUS LIOTHYRONINE FOR CLINICAL (OVERT) HYPOTHYROIDISM

- For GRADE evaluation of interventions for Hypothyroidism (primary), see table, p 12 .
- We found no evidence from RCTs that levothyroxine plus liothyronine improves symptoms compared with levothyroxine alone.
- Treating clinical (overt) hypothyroidism with thyroid hormone (levothyroxine) can induce hyperthyroidism and reduce bone mass in postmenopausal women, and can increase the risk of atrial fibrillation.

Benefits and harms

Levothyroxine (L-thyroxine) plus liothyronine versus placebo:

We found no systematic review or RCTs.

Levothyroxine (L-thyroxine) plus liothyronine versus L-thyroxine alone:

We found two systematic reviews, one with a search date of 2005. [10] The second review had a later search date but included no further RCTs. [11]

Symptom severity

Levothyroxine plus liothyronine compared with levothyroxine alone Levothyroxine plus liothyronine seems no more effective at reducing body pain and fatigue (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[10] Systematic review	465 people 4 RCTs in this analysis	**Body pain** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute results not reported	SMD 0 95% CI –0.34 to +0.35	⟷	Not significant
[10] Systematic review	173 people 6 RCTs in this analysis	**Fatigue** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute results not reported	SMD –0.12 95% CI –0.33 to +0.09	⟷	Not significant

No data from the following reference on this outcome. [11]

Quality of life

Levothyroxine plus liothyronine compared with levothyroxine alone Levothyroxine plus liothyronine seems no more effective at improving quality of life (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[10] Systematic review	532 people 7 RCTs in this analysis	**Quality of life** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported	SMD +0.03 95% CI –0.09 to +0.15	⟷	Not significant

No data from the following reference on this outcome. [11]

Cognitive function

Levothyroxine plus liothyronine compared with levothyroxine alone Levothyroxine plus liothyronine seems no more effective at improving cognitive function, anxiety, and depression (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cognitive function					
[10] Systematic review	646 people 11 RCTs in this analysis	**Depression** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported	SMD +0.07 95% CI –0.20 to +0.34	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[10] Systematic review	Number of people not reported 7 RCTs in this analysis	**Anxiety** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported	SMD 0 95% CI –0.12 to +0.11	⟷	Not significant
[10] Systematic review	386 people 5 RCTs in this analysis	**Cognitive function (Symbol Digit Modalities Test)** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported The Symbol Digit Modalities Test assesses cognitive efficiency and the ability to undertake a novel task	WMD +0.15 95% CI –0.79 to +1.08	⟷	Not significant
[10] Systematic review	571 people 8 RCTs in this analysis	**Cognitive function (Digit Span Sub-Test [forward sub-test])** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported The Digit Span Sub-Test of the Wechsler Adult Intelligence Scale III assesses immediate auditory memory and concentration	WMD –0.02 95% CI –0.25 to +0.22	⟷	Not significant
[10] Systematic review	571 people 8 RCTs in this analysis	**Cognitive function (Digit Span Sub-Test [backward sub-test])** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported The Digit Span Sub-Test of the Wechsler Adult Intelligence Scale III assesses immediate auditory memory and concentration	WMD –0.07 95% CI –0.30 to +0.15	⟷	Not significant

No data from the following reference on this outcome. [11]

Cardiac function

No data from the following reference on this outcome. [10] [11]

Changes in body composition

No data from the following reference on this outcome. [10] [11]

Prevention of progression from subclinical to overt hypothyroidism

No data from the following reference on this outcome. [10] [11]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[10] Systematic review	1216 people 11 RCTs in this analysis	**Adverse effects** with L-thyroxine plus liothyronine (L-tri-iodothyronine) with L-thyroxine alone Absolute numbers not reported The review did not report details of individual adverse effects	RR 1.19 95% CI 0.63 to 2.24	⟷	Not significant

No data from the following reference on this outcome. [11]

Further information on studies

[10] The review pooled data. Seven included RCTs were crossover in design, and 4 included RCTs were parallel in design. The RCTs included in the review ranged in size from 13 to 697 people. The review found no significant difference between groups in thyroid function tests or serum lipid levels. The review concluded that monotherapy with L-thyroxine should remain the standard treatment for hypothyroidism. The RCTs included used widely different combinations/regimens in the L-thyroxine plus liothyronine arms of the trials.

Comment: None.

QUESTION What are the effects of treatments for subclinical hypothyroidism?

OPTION LEVOTHYROXINE (L-THYROXINE) FOR SUBCLINICAL HYPOTHYROIDISM

- For GRADE evaluation of interventions for Hypothyroidism (primary), see table, p 12 .
- We don't know how effective levothyroxine is in treating people with subclinical hypothyroidism, as trials have been too small to detect any clinically relevant improvements in outcomes.
- Treating subclinical hypothyroidism with thyroid hormone can induce hyperthyroidism and reduce bone mass in postmenopausal women, and can increase the risk of atrial fibrillation.

Benefits and harms

Levothyroxine replacement versus placebo or non-treatment:

We found one systematic review (search date 2006) comparing levothyroxine replacement versus placebo (11 RCTs) or no treatment (1 RCT) in adults with subclinical hypothyroidism. RCTs included in the review had a minimum follow-up of 1 month. [12] We found one additional RCT that assessed the effects of L-thyroxine on cardiac function. [13]

Symptom severity

Compared with placebo or no treatment We don't know whether levothyroxine is more effective at reducing symptom severity in people with subclinical hypothyroidism (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom severity					
[12] Systematic review	24 people Data from 1 RCT	**Improved symptoms** with levothyroxine with placebo Absolute numbers not reported	RR 2.5 95% CI 0.80 to 7.83	⟷	Not significant
[12] Systematic review	155 people 4 RCTs in this analysis	**Symptom scores** with levothyroxine with placebo Absolute numbers not reported	SMD –0.30 95% CI –0.62 to +0.02 P = 0.48	⟷	Not significant
[12] Systematic review	164 people 3 RCTs in this analysis	**Change in symptom scores** with levothyroxine with placebo Absolute numbers not reported	SMD –0.24 95% CI –0.54 to +0.07 P = 0.70	⟷	Not significant

No data from the following reference on this outcome. [13]

Cognitive function

Compared with placebo or no treatment Levothyroxine may be more effective at improving cognitive function in people with subclinical hypothyroidism, but we don't know whether it is more effective at improving depression (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cognitive function					
[12] Systematic review	36 people Data from 1 RCT	**Cognitive function** with levothyroxine with placebo Absolute numbers not reported	SMD 2.40 95% CI 0.30 to 4.50	○○○	levothyroxine
[12] Systematic review	68 people Data from 1 RCT	**Emotional function tests of depressed mood** with levothyroxine with placebo Absolute numbers not reported	SMD +0.06 95% CI –0.41 to +0.54 P = 0.81	⟷	Not significant

No data from the following reference on this outcome. [13]

Quality of life

Compared with placebo or no treatment Levothyroxine seems no more effective at improving quality of life or health-related quality of life in people with subclinical hypothyroidism (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[12] Systematic review	34 people Data from 1 RCT	**Proportion of people improved on general health question-naire** 12/20 (60%) with levothyroxine 11/14 (78%) with placebo	RR 0.76 95% CI 0.49 to 1.20 P = 0.24	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[12] Systematic review	31 people Data from 1 RCT	**Changes in health-related quality of life** with levothyroxine with placebo Absolute numbers not reported	SMD +0.08 95% CI –0.62 to +0.79 P = 0.98	⟷	Not significant

No data from the following reference on this outcome. [13]

Cardiac function

Compared with placebo Levothyroxine seems more effective at improving left ventricular function at 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Cardiac function					
[13] RCT	40 people with increased TSH, and normal T_4 and T_3 for least 1 year	**Left ventricular function (increased isovolumic relaxation time) , 6 months** with L-thyroxine (50 micrograms/day) with placebo Absolute numbers not reported Cardiac function was assessed by conventional two-dimensional Doppler echocardiography and ultrasonic videodensitometry	P <0.03	○○○	L-thyroxine
[13] RCT	40 people with increased TSH, and normal T_4 and T_3 for least 1 year	**Left ventricular function (peak A) , 6 months** with L-thyroxine (50 micrograms/day) with placebo Absolute numbers not reported Cardiac function was assessed by conventional two-dimensional Doppler echocardiography and ultrasonic videodensitometry	P <0.05	○○○	L-thyroxine
[13] RCT	40 people with increased TSH, and normal T_4 and T_3 for least 1 year	**Left ventricular function (pre-ejection/ejection time ratio) , 6 months** with L-thyroxine (50 micrograms/day) with placebo Absolute numbers not reported Cardiac function was assessed by conventional two-dimensional Doppler echocardiography and ultrasonic videodensitometry	P <0.03	○○○	L-thyroxine
[13] RCT	40 people with increased TSH, and normal T_4 and T_3 for least 1 year	**Left ventricular function (cyclic variation index) , 6 months** with L-thyroxine (50 micrograms/day) with placebo Absolute numbers not reported Cardiac function was assessed by conventional two-dimensional	P <0.05	○○○	L-thyroxine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Doppler echocardiography and ultrasonic videodensitometry			

No data from the following reference on this outcome. [12]

Changes in body composition

No data from the following reference on this outcome. [12] [13]

Prevention of progression from subclinical to overt hypothyroidism

No data from the following reference on this outcome. [12] [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[12] Systematic review	138 people 4 RCTs in this analysis	**Adverse effects** with levothyroxine with placebo Absolute numbers not reported See adverse effects of levothyroxine for clinical hypothyroidism, p 3	The RCTs that reported on adverse effects found no significant differences between groups No further data reported	⟷	Not significant

No data from the following reference on this outcome. [13]

Further information on studies

Comment: None.

GLOSSARY

T_3 is used as an abbreviation for endogenous tri-iodothyronine in medical and biochemical reports.

T_4 is used as an abbreviation for endogenous thyroxine in medical and biochemical reports.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

SUBSTANTIVE CHANGES

Levothyroxine (L-thyroxine) for subclinical hypothyroidism One systematic review added comparing thyroid hormone replacement versus placebo or no treatment. [12] The review found that hormone replacement improved general symptoms and cognitive function compared with placebo or no treatment, but found no difference between groups for quality of life or health-related quality of life. [12] Categorisation unchanged (Unknown effectiveness).

Levothyroxine (L-thyroxine) plus liothyronine for clinical (overt) hypothyroidism One systematic review added comparing L-thyroxine alone versus a combination of L-thyroxine plus liothyronine (L-tri-iodothyronine) in people with primary hypothyroidism. [11] The review added no further data than already included and also found no difference between groups in psychiatric symptoms. [11] Categorisation unchanged (Unlikely to be beneficial).

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Competing interests: BN declares that she has no competing interests.
The following previous contributor of this review, Lars Kristensen, would also like to be acknowledged.

GRADE Evaluation of interventions for Hypothyroidism (primary).

Important outcomes	Cardiac function, Changes in body composition, Cognitive function, Prevention of progression from subclinical to overt hypothyroidism, Quality of life, Symptom severity								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for clinical (overt) hypothyroidism?									
at least 6 (at least 465) [10]	Symptom severity	Levothyroxine (L-thyroxine) plus liothyronine versus L-thyroxine alone	4	0	0	–1	0	Moderate	Directness point deducted for multiple/different regimens used
7 (532) [10]	Quality of life	Levothyroxine (L-thyroxine) plus liothyronine versus L-thyroxine alone	4	0	0	–1	0	Moderate	Directness point deducted for multiple/different regimens used
11 (at least 646) [10]	Cognitive function	Levothyroxine (L-thyroxine) plus liothyronine versus L-thyroxine alone	4	0	0	–1	0	Moderate	Directness point deducted for multiple/different regimens used
What are the effects of treatments for subclinical hypothyroidism?									
at least 4 (at least 164) [12]	Symptom severity	Levothyroxine replacement versus placebo or non-treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and unclear outcome measures
2 (104) [12]	Cognitive function	Levothyroxine replacement versus placebo or non-treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and unclear outcome measures
2 (65) [12]	Quality of life	Levothyroxine replacement versus placebo or non-treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (40) [13]	Cardiac function	Levothyroxine replacement versus placebo or non-treatment	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.